Journal of Cystic Fibrosis 11 (2012) 393 – 397

www.elsevier.com/locate/jcf

Original Article

LDL-cholesterol and insulin are independently associated with body mass index in adult cystic fibrosis patients

Lise Coderre [a, e], Christophe Fadainia [a], Linda Belson [a, b], Virginie Belisle [a], Sophie Ziai [a, b], Geneviève Maillhot [e, f], Yves Berthiaume [c, e], Rémi Rabasa-Lhoret [a, b, c, d, e,*]

[a] *Institut de recherches cliniques de Montréal, Platform for Research on Obesity, Metabolism, and Diabetes (PROMD), Montréal, Québec, Canada*
[b] *Department of Nutrition, Université de Montréal, Montréal, Québec, Canada*
[c] *Research Centre & Cystic Fibrosis Clinic, Centre hospitalier de l'Université de Montréal (CHUM)-Hôtel-Dieu, Montréal, Québec, Canada*
[d] *Montreal Diabetes Research Center (MDRC) & Endocrine division, CHUM, Montréal, Québec, Canada*
[e] *Department of Medicine, Université de Montréal, Montréal, Québec, Canada*
[f] *Research Center, CHU Sainte-Justine, Montréal, Québec, Canada*

Received 22 June 2011; received in revised form 9 February 2012; accepted 14 March 2012
Available online 12 April 2012

Abstract

Background: The median life expectancy of cystic fibrosis (CF) patients has increased dramatically over the last few years and we now observe a subset of patients with a body mass index (BMI) exceeding 25 kg/m^2. The aim of this study was to characterize these individuals and to identify factors associated with higher BMI.
Methods: This is a cross sectional study including 187 adult CF subjects. Percent predicted forced expiratory volume in 1 s (%FEV$_1$), blood lipid profiles as well as fasting glucose and insulin levels were evaluated. Subjects also had an oral glucose tolerance test (OGTT) and the area under the curve (AUC) for glucose and insulin was calculated. CF subjects were then stratified according to the following BMI categories: underweight: BMI ≤ 18.5 kg/m^2; normal weight: 18.5 kg/m^2 < BMI < 25 kg/m^2; and overweight or obese: BMI ≥ 25 kg/m^2.
Results: Overweight subjects were older and less likely to have enzyme supplementation compared to the other two groups. Furthermore, this group exhibits higher levels of fasting insulin, total and LDL-cholesterol as well as insulin AUC. Further analyses demonstrated that BMI correlated with %FEV$_1$, fasting insulin, insulin AUC, total cholesterol, LDL-cholesterol and the ratio of HDL-cholesterol to total cholesterol and that %FEV$_1$, insulin AUC and LDL-cholesterol were independent associated with BMI.
Discussion: Overweight CF subjects have higher fasting insulin and insulin AUC as well as total and LDL-cholesterol. Furthermore, we also demonstrated that LDL-cholesterol, insulin AUC are independently associated with BMI in a population of adult CF subjects.

Keywords: LDL-cholesterol; Insulin; Body mass index; Cystic fibrosis; Lung function

1. Introduction

Cystic fibrosis (CF) is the most common lethal autosomal disease affecting Caucasian individuals with an incidence of 1 per 3608 in live births in Canada in 2000 [1]. Pulmonary disease is the primary clinical manifestation and the major cause of death in CF patients. In addition, approximately 90% of CF patients have exocrine pancreatic insufficiency, leading to malabsorption, malnutrition, poor weight gain and low body mass index (BMI) [2] Numerous studies have shown the strong positive relationship between BMI and lung function [3,4]. Furthermore, BMI is an important predictor of survival in CF patients [5,6]. Thus, factors associated with higher BMI are of critical importance for CF outcomes. With the advancement of clinical care and nutritional monitoring, most CF patients now reach their target weight and the

* Corresponding author at: Institut de recherches cliniques de Montréal, 110 avenue des Pins Ouest, Montréal, QC, Canada H2W 1R7. Tel.: +1 514 987 5666; fax: +1 514 987 5670.
E-mail address: remi.rabasa-lhoret@ircm.qc.ca (R. Rabasa-Lhoret).

1569-1993/$ -see front matter © 2012 Published by Elsevier B.V. on behalf of European Cystic Fibrosis Society.
doi:10.1016/j.jcf.2012.03.006

median life expectancy of CF subjects has increased to above 40 years old in Canada [7]. Furthermore, we now observe the emergence of a subset of CF patients who are considered overweight or obese (BMI ≥ 25 kg/m^2). However, whether these individuals have a better or worse clinical and metabolic profile compared to normal weight CF individuals is unknown at present. The aim of this study was to characterize overweight CF subjects and to identify factors associated with higher BMI.

2. Subjects and methods

2.1. Subjects

Baseline data of the first 187 subjects included in the Montreal Cystic Fibrosis Cohort (MCFC) were used for the analysis. The MCFC was established in 2004 as part of an ongoing systematic screening program to detect CF related diabetes (CFRD) using the oral glucose tolerance test (OGTT) [8]. The main objective of this prospective observational cohort is to study mechanisms associated with glucose intolerance as well as the association of pre-diabetic states with CF outcomes. The protocol was approved by the Research Ethics Committee of the Centre hospitalier de l'Université de Montréal and all participants gave informed written consent before participation.

CF subjects included in the analysis were over 18 years of age and with no previously diagnosed diabetes. Exclusion criteria were exacerbation in the previous month defined by changes in sputum production (volume, color, consistency), new or increased hemoptysis, cough, increased dyspnea, fatigue or lethargy, fever, anorexia, sinus pain, a 10% decrease in pulmonary function determined by forced expiratory volume in 1 s (FEV_1) from previous values (recorded every 3 months), intravenous antibiotic treatment, the use of medications or conditions that interfere with glucose metabolism, steroids (oral or intravenous), growth hormone, megace, transplantation or pregnancy. Exacerbation was identified on the same day by a trained CF pneumologist blinded to the metabolic parameters.

2.2. CF status and anthropometric data

Pulmonary function (FEV_1 (L/sec) and predicted %FEV_1) was measured by spirometry on the day of the OGTT (Medgraphic 1870, St-Paul, MN, USA). Pancreatic insufficiency was defined by current enzyme supplementation. CF genotypes were extracted from the medical files. Numerous studies have shown a strong correlation between genotype and exocrine pancreatic function. They also showed that the milder mutation has a dominant phenotypic effect [9,10]. Thus, patients abhorring severe mutation on both alleles were classified as "severe" while patients having as least one allele associated with a milder phenotype were classified as "moderate to mild" (http://www.genet.sickkids.on.ca and [9–12]). Patients abhorring unknown mutations were excluded from the statistical analysis.

Body weight was measured using an electronic scale (Tanita Corporation Arlington heights, IL, USA) and standing height by a wall stadiometer. BMI was calculated using weight in kilograms divided by height in meters (kg/m^2).

2.3. Oral glucose tolerance test (OGTT)

All subjects underwent a 2-h OGTT. After an overnight fast, they ingested, in less than 5 min, a glucose solution: 1.75 g/kg of body weight to a maximum of 75 g according to the Canadian Diabetes Association guidelines [13]. Plasma glucose and insulin concentrations were measured at 0, 30, 60, 90 and 120 min. Plasma glucose was determined immediately in duplicate by the glucose oxidase method (Beckman Coulter, Fullerton, CA, USA). Insulin levels were determined in duplicate using human insulin Radio Immuno Assay (Linco Research Inc. St-Charles, MO, USA).

2.4. Biochemical dosages

Total cholesterol, triglycerides and HDL-cholesterol were measured by enzymatic reaction (ADVIA1650, Bayer Health Care Diagnostics). Total cholesterol, HDL-cholesterol and triglycerides were used in the Friedewald formula to calculate LDL-cholesterol concentration [14].

2.5. Statistical analysis

Data are presented as mean ± standard deviation (SD). Glucose and insulin AUC were calculated using Graphpad Prism 4.0 for Windows. Subjects were stratified by BMI as previously described [15,16]: *underweight*: BMI ≤ 18.5 kg/m^2; *normal* weight: 18.5 kg/m^2 < BMI < 25 kg/m^2; and *overweight* or *obese*: BMI ≥ 25 kg/m^2.

Group differences were determined by analyses of variance (ANOVA) or CHI square as appropriate. Associations were determined using Pearson correlation (n = 127 subjects). We then used hierarchical linear regression to examine the contribution of these variables to BMI. The following variables were associated with BMI and were thus included in the first model: age, genotype, enzyme supplementation and sex. We then assessed additional models for the independent contribution of variables that were significantly associated with BMI. The statistical analysis was performed with SPSS for Windows (Version 16.0 SPSS, Chicago, IL). Significance was accepted at $p < 0.05$.

3. Results

As shown in Tables 1 and 3, the 187 subjects displayed important variation in lung function, BMI and metabolic profile. As shown in Table 2, analysis of BMI distribution showed that 75% of our cohort had normal BMI while 13% were underweight, 11% were overweight and one subject was obese (BMI = 30.6). We did all analysis with or without the obese subject and observed similar results. We did not find any significant difference among BMI categories for sex. On the other hand, we observed significant differences among the groups for enzyme supplementation ($p = 0.01$) and genotype ($p = 0.048$). As reported previously [17,18], we found a strong association between genotype and enzyme supplementation ($p = 0.001$). Thus, more than 90% of underweight subjects had severe mutation on both alleles as well as enzyme supplementation. In contrast, the prevalence of

Table 1
Clinical characteristics of cystic fibrosis subjects (n=187).

Characteristics	Mean±SD	Range
Age (years)	26.3±7.6	18–49
%FEV_1	70±21	19–119
Sex (% women)	48.1	
Genotype		
Severe (%)	71.7	
Mild to moderate (%)	14.4	
Unclassified (%)	13.9	
Pancreatic enzyme supplementation (n=184)	83	
Body mass index (kg/m^2)	21.5±3.0	13.1–30.6

FEV_1: Forced Expiratory Volume in 1 s.

severe mutation and enzyme supplementation in the overweight group was 54% and 62%, respectively. Furthermore, overweight subjects were significantly older than either underweight or normal weight individuals while underweight subjects had worse lung function compared to the two other groups (Table 2).

As shown in Table 3, overweight subjects exhibited higher fasting insulin levels, insulin AUC, fasting cholesterol levels as well as a ratio of cholesterol/HDL-cholesterol compared to the other two groups. Furthermore, we observed a significant progressive increase in the level of LDL-cholesterol with increasing BMI categories. It should be noted, however, that the cholesterol values remain in the normal range for all groups [19].

We next examined the association between BMI and various metabolic parameters using Pearson correlations. BMI correlated positively with age ($r=0.33$; $p<0.01$), %FEV_1 ($r=0.32$; $p<0.01$), fasting insulin ($r=0.20$; $p<0.01$); insulin AUC ($r=0.20$; $p<0.01$), triglycerides ($r=0.17$; $p<0.05$), total cholesterol ($r=0.37$; $p<0.01$) and LDL-cholesterol ($r=0.42$; $p<0.01$) and the ratio of total cholesterol/HDL-cholesterol ($r=0.41$; $p<0.01$). Except for triglycerides, these correlations remained statistically significant after correcting for age, genotype, sex, and enzyme supplementation. We next determined which of these variables were independently associated with BMI in our cohort. As shown in Table 4, LDL-cholesterol, %FEV_1, and insulin AUC remained independently associated with BMI after correcting for sex, age, genotype, and enzyme supplementation in CF subjects. Together, these variables explained 35% of the variance of BMI.

Table 2
Clinical characteristics of cystic fibrosis subjects by BMI category.

Characteristics	BMI (kg/m^2)		
	≤18.5	Between 18.5 and 25	≥25
	n=25	n=141	n=21
Age (years)	23.8±5.2	25.8±7.6	32.5±7.8 [a,b]
%FEV_1	56±19	71±21 [a]	79±21 [a]
Sex (men/women)	11/14	72/69	14/7
Genotype (%)			
Severe (%)	92	70.9	54.2
Mild to moderate (%)	4	14.2	28.6
Unclassified (%)	4	14.9	19
Enzyme supplementation (%)	95.8	83.5	61.9

Genotype $p=0.048$.
Pancreatic supplementation $p=0.01$.
[a] $p<0.05$ significantly different compared to subjects with BMI ≤ 18.5.
[b] $p<0.05$ significantly different compared to subjects with BMI between 18.5 and 25.

Table 3
Metabolic characteristics of cystic fibrosis subjects by categories of BMI.

Characteristics	BMI (kg/m^2)			Range
	≤18.5	Between 18.5 and 25	≥25	
	n=25	n=141	n=21	
Fasting glucose (mmol/l)	5.7±1.1	5.4±0.8	5.4±0.4	3.8–9.3
Glucose 120 min (mmol/l)	9.1±4.9	7.9±3.1	7.8±2.6	2.3–18.8
Glucose AUC	528±261	466±231	411±189	89–1199
Fasting insulin (pmol/l)	8.9±2.5	9.7±4.0	11.9±3.3 [a]	2.00–27.6
Insulin AUC	2827±1393	3467±2114	4837±2192 [a,b]	335–11,906
Triglycerides (mmol/l)	1.01±0.08	1.05±0.04	1.26±0.14	0.35–3.24
Cholesterol (mmol/l)	3.1±0.8	3.5±1.0	4.2±0.8 [a,b]	1.7–7.1
HDL-C (mmol/l)	1.2±0.4	1.2±0.3	1.2±0.2	0.59–2.28
LDL-C (mmol/l)	1.4±0.6	1.9±0.8 [a]	2.4±0.8 [a,b]	0.63–4.87
TC/HDL-C	2.63±0.58	3.02±0.71	3.61±0.73 [a,b]	1.6–5.6

[a] $p<0.05$ significantly different compared to subjects with BMI ≤ 18.5.
[b] $p<0.05$ significantly different compared to subjects with BMI between 18.5 and 25.

4. Discussion

Current CF Foundation guidelines recommend that BMI be maintained at ≥ 22 kg/m^2 for women and ≥ 23 kg/m^2 for men [20]. This is slightly higher than the average BMI observed in our cohort which is 21±2.9 and 22±3.0 kg/m^2 for men and women, respectively. Based on these recommendations, only 33% of our subjects are above the recommended BMI, which highlights the importance of identifying factors positively associated with BMI.

In our study, 13% of CF subjects were classified as overweight. This is similar to Kastner-Cole et al. who reported a prevalence of 10% for overweight and obese in CF patients homozygous for delta508 mutation [21]. Approximately 17% of the cohort did not have pancreatic enzyme supplementation, which is in a similar range than the 14% reported by the Canadian Cystic Fibrosis Patient Data Registry Report [7].

Table 4
Stepwise regression analysis of independent predictors of BMI (n=130).

Dependent variable	Step	Predictor	R	R^2	R change	*P* value
BMI	1	Enzyme, sex, age genotype	0.416	0.173	0.173	0.001
BMI	2	%FEV_1	0.516	0.266	0.093	0.001
BMI	3	LDL-cholesterol	0.572	0.327	0.060	0.004
BMI	4	Insulin AUC	0.599	0.359	0.033	0.007

Compared to underweight and normal weight individuals, a higher proportion of overweight individuals abhorred CFTR mutations associated with milder phenotypes and did not have enzyme supplementation. Overweight patients were also characterized by higher levels of fasting insulin, total cholesterol, LDL-cholesterol as well as increased insulin AUC. To our knowledge, this is the first characterization of overweight CF individuals with respect to metabolic parameters and the first demonstration of an independent association between LDL-cholesterol and BMI in CF subjects.

Analysis of the complete study sample showed a strong positive association between $\%FEV_1$ and BMI and showed that BMI is independently associated with $\%FEV_1$. Other studies have demonstrated a similar association in CF individuals [3,4,20] and it has been suggested that lung disease contributes to altered body composition [22,23]. One possible mechanism to this relationship is the increase in resting metabolic rate observed with the progression of lung disease which, when combined with malabsorption and negative caloric balance during periods of infection, may lead to lower BMI [24]. Importantly for CF patients, those who are overweight exhibit reduced probability of death at 5 years compared to those with normal weight [24]. While underweight patients showed lower $\%FEV_1$ compared to the other two groups, we did not observed any significant difference between overweight and normal weight individuals for this parameter. In contrast to children, there seem to be a clinical threshold in CF adults beyond which higher BMI does not translate into higher $\%FEV_1$ [21]. Together, these results highlight the importance of BMI in CF outcome.

Our data highlighted important differences among BMI groups for genotype. Thus, 92% of underweight subjects exhibit mutations associated with severe phenotype while its prevalence was only 54.2% in overweight group. As previously shown [9,11], we observed a strong correlation between CFTR genotype and phenotype of the exocrine pancreas. Thus, the overweight group has a lower proportion of individuals with severe mutation as well as enzyme supplementation compared to the other groups. It should be noted, however, that more than 54.2% of overweight individuals have severe CFTR mutations and of those, 33% are homozygous for the delta508 mutation. This wide variation of BMI between patients bearing identical CFTR mutations suggests that additional factors either genetic or environmental may contribute to the phenotype. Importantly, we observed that subjects with milder phenotypic CFTR mutations also had higher insulin AUC. Whether this difference in insulin AUC are due only to disruption of islet architecture due to fibrosis and fatty infiltration of the pancreas or whether other mechanism such as amyloid deposit or diabetes specific mutations contribute to these difference remains to be investigated. Interestingly, there was no association between fasting insulin and either genotype or enzyme supplementation.

Our results also demonstrated that insulin AUC was independently associated with BMI in CF subjects. Insulin is an important anabolic hormone and recent studies have demonstrated that insulin therapy may prevent BMI loss in patients with CFRD [25]. Similarly, Mohan et al. [26] have reported that insulin administration for 3 years to CFRD subjects lead to improved BMI. Furthermore, there is a significant relationship between insulin AUC and linear growth velocity in CF children [27]. Further studies should further investigate the relationship between insulin and BMI in CF patients.

We observed lower LDL-cholesterol values and reduced $\%FEV_1$ in underweight CF patients. In the complete study sample, we observed a strong positive association between BMI and LDL-cholesterol levels in CF individuals. Furthermore, our analysis revealed that LDL-cholesterol is independently associated with BMI in this population. Low LDL-cholesterol has been observed in critically ill patients [28,29] as well as in individuals with chronic infections and sepsis [30,31]. Furthermore, low cholesterol level is a predictor of mortality in acute kidney injury and in critically ill surgical patients [30,32–34] and it had been suggested that hypocholesterolemia may be used as a marker of disease severity [29,35]. Whether this also apply to CF subjects remains to be demonstrated.

The present study included only CF subjects with *de novo* diabetes to avoid confounding factors such as insulin treatment. Furthermore, our study included mostly CF subjects with mild to moderate lung disease. Therefore, whether our results extend to more severely affected CF patients remain to be investigated.

In conclusion, the present results provide new evidence of the association of BMI with LDL-cholesterol and insulin AUC in a population of adult CF subjects with mild to moderate lung disease. Further studies should examine the association between LDL-cholesterol and insulin levels and BMI in CF in non-diabetic subjects.

Acknowledgements

Special thanks to Stéphanie Potvin, Sylvie Blaquière, Shirley Ferguson, Renée Lévesque and Yung-Chun Chou for their technical assistance. R.R.-L. is a scholar of the «Fonds de recherches en santé du Québec» (FRSQ) and holds the J-A de Sève Chair in Clinical Research. S.Z. has a studentship from the FRSQ and the Canadian Institutes of Health Research (CIHR). This study is supported by an operating grant from the Canadian Cystic Fibrosis Foundation.

References

[1] Dupuis A, Hamilton D, Cole DE, Corey M. Cystic fibrosis birth rates in Canada: a decreasing trend since the onset of genetic testing. J Pediatr Sep 2005;147(3):312–5.
[2] Borowitz D. The interrelationship of nutrition and pulmonary function in patients with cystic fibrosis. Curr Opin Pulm Med Nov 1996;2(6):457–61.
[3] Jarad NA, Higgs S, Jeffcote T, Giles K. Factors associated with reduced FEV1 in adult patients with cystic fibrosis in a relatively affluent area. Chron Respir Dis 2005;2(3):133–7.
[4] Pedreira CC, Robert RG, Dalton V, Oliver MR, Carlin JB, Robinson P, et al. Association of body composition and lung function in children with cystic fibrosis. Pediatr Pulmonol Mar 2005;39(3):276–80.
[5] Snell GI, Bennetts K, Bartolo J, Levvey B, Griffiths A, Williams T, et al. Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. J Heart Lung Transplant Nov 1998;17(11):1097–103.
[6] Courtney JM, Bradley J, Mccaughan J, O'Connor TM, Shortt C, Bredin CP, et al. Predictors of mortality in adults with cystic fibrosis. Pediatr Pulmonol Jun 2007;42(6):525–32.

[7] Canadian Cystic Fibrosis Patient Data Registry Report. http://www.cysticfibrosis.ca/assets/files/pdf/CPDR_ReportE.pdf 2010.
[8] Costa M, Potvin S, Hammana I, Malet A, Berthiaume Y, Jeanneret A, et al. Increased glucose excursion in cystic fibrosis and its association with a worse clinical status. J Cyst Fibros Nov 30, 2007;6(6):376–83.
[9] Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui LC, et al. Genetic determination of exocrine pancreatic function in cystic fibrosis. Am J Hum Genet Jun 1992;50(6):1178–84.
[10] Clain J, Lehmann-Che J, Dugueperoux I, Arous N, Girodon E, Legendre M, et al. Misprocessing of the CFTR protein leads to mild cystic fibrosis phenotype. Hum Mutat Apr 2005;25(4):360–71.
[11] Ooi CY, Dorfman R, Cipolli M, Gonska T, Castellani C, Keenan K, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology Jan 2011;140(1):153–61.
[12] Castellani C, Cuppens H, Macek Jr M, Cassiman JJ, Kerem E, Durie P, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros May 2008;7(3):179–96.
[13] Canadian Diabetes Association Clinical Practice Guidelines. http://www.diabetes.ca/for-professionals/resources/2008-cpg Sep 1, 2008.
[14] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem Jun 1972;18(6):499–502.
[15] Leiter LA, Fitchett DH, Gilbert RE, Gupta M, Mancini GB, McFarlane PA, et al. Cardiometabolic risk in Canada: a detailed analysis and position paper by the cardiometabolic risk working group. Can J Cardiol Mar 2011;27(2):e1–33.
[16] Hollander F. Dietary treatment of adult patients with cystic fibrosis related diabetes. http://www.cfww.org/docs/pub/edition12/03_dietary.pdf Jan 28, 2010.
[17] Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. J Cyst Fibros Mar 2005;4(1):7–26.
[18] Weintraub A, Blau H, Mussaffi H, Picard E, Bentur L, Kerem E, et al. Exocrine pancreatic function testing in patients with cystic fibrosis and pancreatic sufficiency: a correlation study. J Pediatr Gastroenterol Nutr Mar 2009;48(3):306–10.
[19] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA May 16, 2001;285(19):2486–97.
[20] Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc May 2008;108(5):832–9.
[21] Kastner-Cole D, Palmer CN, Ogston SA, Mehta A, Mukhopadhyay S. Overweight and obesity in deltaF508 homozygous cystic fibrosis. J Pediatr Sep 2005;147(3):402–4.
[22] Ionescu AA, Nixon LS, Luzio S, Lewis-Jenkins V, Evans WD, Stone MD, et al. Pulmonary function, body composition, and protein catabolism in adults with cystic fibrosis. Am J Respir Crit Care Med Feb 15, 2002;165(4):495–500.
[23] Ionescu AA, Nixon LS, Evans WD, Stone MD, Lewis-Jenkins V, Chatham K, et al. Bone density, body composition, and inflammatory status in cystic fibrosis. Am J Respir Crit Care Med Sep 2000;162(3 Pt 1):789–94.
[24] Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJ, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax Oct 2001;56(10):746–50.
[25] Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care Oct 2009;32(10):1783–8.
[26] Mohan K, Israel KL, Miller H, Grainger R, Ledson MJ, Walshaw MJ. Long-term effect of insulin treatment in cystic fibrosis-related diabetes. Respiration 2008;76(2):181–6.
[27] Ripa P, Robertson I, Cowley D, Harris M, Masters IB, Cotterill AM. The relationship between insulin secretion, the insulin-like growth factor axis and growth in children with cystic fibrosis. Clin Endocrinol (Oxf) Mar 2002;56(3):383–9.
[28] Vyroubal P, Chiarla C, Giovannini I, Hyspler R, Ticha A, Hrnciarikova D, et al. Hypocholesterolemia in clinically serious conditions—review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub Dec 2008;152(2):181–9.
[29] Dunham CM, Fealk MH, Sever III WE. Following severe injury, hypocholesterolemia improves with convalescence but persists with organ failure or onset of infection. Crit Care Dec 2003;7(6):R145–53.
[30] Vermont CL, den BM, Kakeci N, de Kleijn ED, de Rijke YB, Joosten KF, et al. Serum lipids and disease severity in children with severe meningococcal sepsis. Crit Care Med Jul 2005;33(7):1610–5.
[31] Fraunberger P, Schaefer S, Werdan K, Walli AK, Seidel D. Reduction of circulating cholesterol and apolipoprotein levels during sepsis. Clin Chem Lab Med Mar 1999;37(3):357–62.
[32] Guimaraes SM, Lima EQ, Cipullo JP, Lobo SM, Burdmann EA. Low insulin-like growth factor-1 and hypocholesterolemia as mortality predictors in acute kidney injury in the intensive care unit. Crit Care Med Dec 2008;36(12):3165–70.
[33] Chiang CK, Ho TI, Hsu SP, Peng YS, Pai MF, Yang SY, et al. Low-density lipoprotein cholesterol: association with mortality and hospitalization in hemodialysis patients. Blood Purif 2005;23(2):134–40.
[34] Obialo CI, Okonofua EC, Nzerue MC, Tayade AS, Riley LJ. Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure. Kidney Int Sep 1999;56(3):1058–63.
[35] Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgadari A, Gui D, et al. Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. Arch Surg Jun 1996;131(6):641–5.